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RESEARCH ARTICLE

Synthesis of Various Cynuric Chloride Based Pyrimidones And Their Antimicrobial Activity

Jagdish Kanjibhai Solanki[*1], *Dr. Rakeshkumar*[2], *Dr. Kartik B. Vyas*[3]

[1&2]Department of Chemistry, Shri Jagdish Prasad Jhabarmal Tibrewala University, Vidyanagari, Jhunjhunu, Rajasthan – 333001 (India)

[3]Department of Chemistry, Sheth L.H. Science College, Mansa, Gujarat (India)

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ABSTRACT

Synthesis of cynuric chloride based various chalcones A1-A19 by condensation reaction of Cyanuric chloride with 1-(4-aminophenyl)ethanone to yields product 1-(4-(4,6-dichloro-1,3,5-triazin-2-ylamino)phenyl)ethanone which upon condensation with various aromatic aldehyde. All prepared chalcones were further reflux with urea to give pyrimidines B1-B19. Characterization of all synthesized pyrimidones were done using various spectroscopic techniques such as 1HNMR, 13CNMR, IR, MASS. Biological evaluation of all prepared pyrimidones were done using against two gram positive bacteria such as Staphylococcus aureus, Bacillus megaterium and two gram negative bacteria Escherichia coli, Proteus vulgaris. Most of the synthesized products exhibited moderate to good potency against bacteria as compared to standard drugs.

KEYWORDS

Pyrimidone, Cyanuric Chloride, Chalcone, Aldehydes, Antimicrobial Activity, Urea, Spectroscopy

INTRODUCTION

Chemistry plays an important role in our daily lives. Food and drink has been made safe to consume; the whole area of pharmaceuticals has allowed the development and synthesis of new medicines for illnesses and diseases; the development of cosmetics has empowered us to prettify; all as a result of chemistry. However, in the chemical industry, huge volumes of hazardous wastes are released to the air, water and land every hour.

*Address for Correspondence:

Jignesh Solanki,
Department of Chemistry,
Shri Jagdish Prasad Jhabarmal Tibrewala University,
Vidyanagari,
Jhunjhunu,
Rajasthan – 333001

In particular, solvents are used in large quantities in chemical and pharmaceutical industries. Therefore, solvents define a major role in the environment pollution and also effect on safety and health problems. The constantly increasing air pollution has brought about changes in the global climate. The inspiration towards clean technology in the chemical industry is requirement of a high level of innovation and new technology in waste reduction. The idea of "green" solvents expresses the goal to minimize the environmental pollution resulting from the use of solvents in chemical production. To overcome these problems four directions towards the green solvents have been developed: (i) Replacement of hazardous solvents by ones that show better EHS (environmental, health and safety) properties, such as increased

biodegradability or reduced ozone depletion potential; (ii) Use of "bio-solvents" i.e. solvents produced from renewable resources such as ethanol produced by fermentation of sugar-containing feeds or starchy feed materials. This replacement leads to an avoidance of fuel CO_2 emissions to the environment; (iii) Replacement of organic solvents either with supercritical fluids that are environmentally friendly e.g. the use of supercritical CO_2 in polymer processing to avoid the use of chlorofluorocarbons, and thus reduces ozone depletion; (iv) Use of non-volatile and thermally stable ionic liquids as solvents in place of traditional solvents, most of which are volatile organic compounds (VOCs). Replacement of conventional solvents by ionic liquids would prevent the emission of VOCs which are major source of environmental pollution. Ionic liquids can be designed to be environmentally benign, with large potential benefits for sustainable chemistry. On the other hand, for many chemical processes a major adverse effect to the environment is the consumption of energy for heating and cooling.

Methods and Materials

Chemicals and Reagents

All chemicals used were of laboratory reagent grade and used without further purification**.** Various aldehydes, pyridine, 1-chloro-4-methyl benzene, 1-(4-aminophenyl)ethanone urea, NaOH and ethanol were used as received from Merck, Mumbai, India.

Experimental

Bruker Avance-400 instrument was used for Proton NMR study and 100MHZ frequency instrument was used for 13C NMR. Parts per million unit was used to expressed chemical shift value. ABB Bomem Inc. FT-IR 3000 Spectrophotometer was used for Infrared Spectral study. Data obtained was expressed in cm-1 unit. Shimadzu LCMS-2010 was used for MASS spectral analysis. Perkin Elmer-2400 Series II CHNS/O Elemental Analyzer was used for Composition measurement.

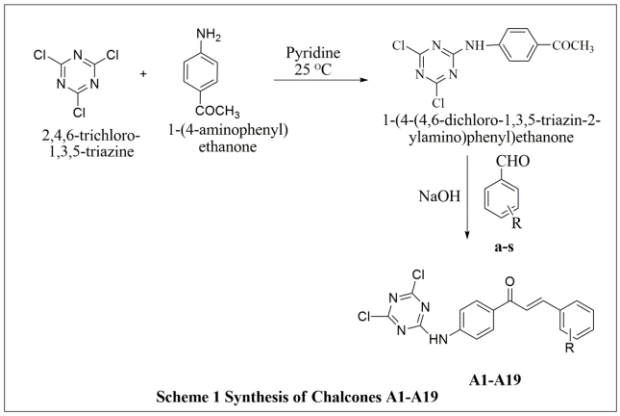
Method of Synthesis

Synthesis of 1-(4-(4,6-dichloro-1,3,5-triazin-2-ylamino)phenyl)ethanone

In a 250 ml round bottom flask, Cyanuric Chloride (0.1 mol) and1-(4-aminophenyl)ethanone (0.1 mol) dissolved in pyridine (50 ml) with constant shaking maintaining the temperature below 25°C. After the completion of dissolution, the mixture was refluxed for 1.5 hr. then it was cooled and poured into crushed ice. Solid was separated by filtration and crystalline from ethanol.

Synthesis of various chalcones A1-A19

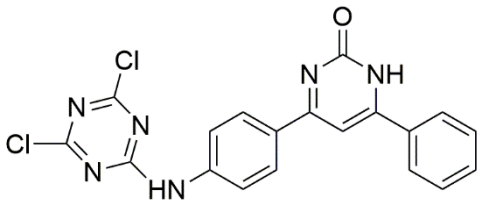
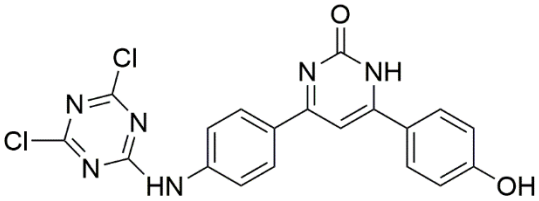
To a well stirred solution of 1-(4-(4,6-dichloro-1,3,5-triazin-2-ylamino)phenyl)ethanone (0.01 mol) in ethanol (40 ml), 40% sodium hydroxide (40 ml) and aromatic aldehyde (0.01 mol) was added drop wise at 0^{o}C). After the completion of addition, the mixture was stirred for further 2-3 hours and left overnight. The contents were poured into ice water and crystallized from ethanol (**Scheme 1**).



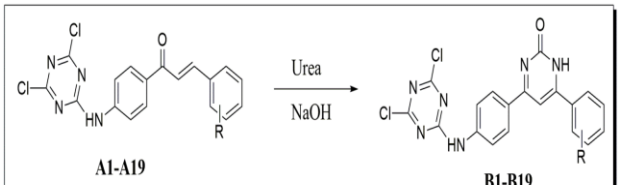
Scheme 1 Synthesis of Chalcones A1-A19

Synthesis of Pyrimidones

Take chalcones (0.01 mol) in 250 ml RBF, add 0.01 mol urea, 40 ml ethanol and 40 ml 40%

Compound code: B1	
Molecular formula: $C_{19}H_{12}Cl_2N_6O$	
M. P. (°C): 215	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	9.3 (NH, s), 8.3 (NH, s), 6.86-8.40 (10H, Ar-H, complex).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	128.2, 129.4, 130.3, 131.6, 139.2, 143.6, 151.8, 153.6, 155.1, 160.8, 170.1, 170.3.
IR cm^{-1} (KBr):	3441, 3320, 3149, 3020, 1660, 1592, 1569, 744.
Mass (M+1):	410.0
Elemental analysis:	**Calculated (%):** C: 55.49; H: 2.94; N:20.44.
	Found (%) : C: 55.62; H: 2.84; N: 20.62
Compound code: B2	
Molecular formula: $C_{19}H_{12}Cl_2N_6O_2$	
M. P. (°C): 235	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	9.2 (NH, s), 8.6 (NH, s), 3.2 (1H, s, OH group), 6.86-8.30 (9H, Ar-H, complex).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	128.9, 129.4, 130.3, 131.6, 140.2, 143.6, 151.8, 153.6, 155.1, 160.8, 170.1, 170.3.
IR cm^{-1} (KBr):	3441, 3350, 3320, 3149, 3020, 1660, 1592, 1569, 744.
Mass (M+1):	426.0
Elemental analysis:	**Calculated (%):** C: 53.41; H: 2.83; N:19.67.
	Found (%) : C: 53.62; H: 2.89; N: 20.58

NaOH to this mixture solution. Reflux the entire mixture for 30-50 minutes to produce Primidone**. C**ompletion of reaction was monitored by TLC (**Scheme 2)**.



Scheme 2 Synthesis of Pyrimidines B1-B19

Characterization

B1 & B2 compounds of the series is taken as the representative compound. In the ^{1}H NMR spectrum the characteristic signals due to each protons and functional groups with protons are well described on the basis of shielding and deshielding effects. The signal due to aromatic proton of compound was observed in more downfield region at chemical shift value around 6 to 8 ppm. $^{1}HNMR$, $^{13}CNMR$, IR, MASS spectroscopic data of B**1 & B2** compounds shown below.

Result and Discussion

Table 1.1 Data showing synthesis of Pyrimidone B1-B19

Sr. No.	Compounds Code	R	Reaction Time[a] (min)	% Yield[b]
1	**B1**	-H	30	72
2	**B2**	4-OH	35	72
3	**B3**	3-OH	35	68
4	**B4**	2-OH	35	75
5	**B5**	2-OCH_3	40	68
6	**B6**	4-OCH_3	40	67
7	**B7**	2-Cl	35	80
8	**B8**	4-Cl	35	80
9	**B9**	3-Cl	35	75
10	**B10**	2-NO_2	25	83
11	**B11**	4-NO_2	25	83
12	**B12**	3-NO_2	25	82
13	**B13**	3-Br	35	78
14	**B14**	2- Br	35	75
15	**B15**	4- Br	35	78
16	**B16**	3, 4-$(OCH_3)_2$	45	72
17	**B17**	3,4,5-$(OCH_3)_3$	45	72
18	**B18**	2-furfuryl[c]	30	82
19	**B19**	2-Thineyl[c]	30	80

[a]Reaction is monitored by TLC, [b]Isolated yield & [c]Names of aldehyde groups

From the Table 1.1 show the various condensation product of condensation reaction between compounds A1-A19 and Urea. It clearly indicates that the compounds bearing electron withdrawing group are synthesized in shorter reaction time as compared to compounds bearing electron donating group. Compounds B10-B12 bearing electron withdrawing were synthesized in 27 min as shorter time as compared to compound B16 and B17 bearing electron donating group in 47 min.

Antimicrobial Activity

Preparation of Media:

For bacterial activity nutrient agar is used. Nutrient agar is prepared as follows:
5gm Peptone, 3gm Metal Extract, 5gm NaCl and 15gm Agar-Agar Peptone were mixed in one liter distilled water and heated to dissolve all the ingredients. The medium was stabilized in autoclave at 15 pound pressure at 125oC for

20 minutes. The medium was cooled down to 45oC and 20 ml poured in sterilized Petri-dish. The pH of the medium was adjusted between 7.0 to 7.5. The culture of the above organism was prepared in nutrient broth dissolved in distilled water. The content of nutrient broth is:

Beef extract : 10 gm
Peptone : 10 gm
Sodium chloride : 5 gm

After sterilizing the above media, it was used for the culture purpose. The culture was ground at 37oC in incubator. With the help of swab, the culture was spread over the agar plates, under specific condition 5 mm diameter paper discs were prepared and were sterilized in autoclave. The solution of the test compound was kept over these paper discs with the help of micropipette. These discs were dried to remove the solvent. Sterile test compound coated by discs were kept in Petri dish containing culture media. The
discus was pressed to sterile on media and Petri dishes were incubated for 24 hours at 37oC. After the incubations the zone of inhibition was measured.

Experimental Data of Antimicrobial Study

(I) **Against *Staphylococcus aureus*:**

Maximum activity were found in compounds (B18, B19) zone of inhibition-13.0 m.m. and minimum activity were found in compounds (B7, B11) zone of inhibition -6.0 m.m

(II) **Against *Bacillus megaterium*:**

Maximum activity were found in compounds (B13, B17) zone of inhibition -14.0 m.m where

Table 1.2 Antibacterial Activities of COMPOUND B1-B19

Samples	*S.aureus* (+Ve)	*B.megaterium*	*E.coli* (-Ve)	*P.vulgaris* (-Ve)
B1	8	5	4	7
B2	6	7	8	8
B3	8	6	10	10
B4	3	3	6	4
B5	10	11	7	7
B6	9	6	4	6
B7	8	6	5	10
B8	9	9	10	4
B9	11	11	12	6
B10	9	4	7	6
B11	9	5	4	7
B12	11	7	9	8
B13	10	9	12	6
B14	8	7	8	6
B15	8	8	6	9
B16	9	8	9	4
B17	12	10	12	9
B18	10	12	12	12
B19	10	12	12	11
Ampicillin	**15**	**14**	**17**	**19**
Gentamycin	**16**	**15**	**14**	**16**

as minimum activity were found in compound (B4) zone of inhibition -5.0 m.m.

(III) **Against *Escherichia coli*:**

Maximum activity were found in compounds (B13, B9, B13, B17, B18, B19) zone of inhibition -12.0 m.m and minimum activity were found in compounds (B4) zone of inhibition -3.0 m.m

(IV) **Against *Proteus vulgaris*:**

Maximum activity were found in compound (B9, B13, B17, B18, B19) zone of inhibition -16.0 m.m (near to standard drug) and minimum activity were found in compounds (B4) zone of inhibition 3.0 mm.

CONCLUSION

In conclusion the highly functionalized pyrimidones derivatives (**B1-B19)** were synthesized from various chalcones which is insitu formed from different aromatic aldehydes. All the compounds are well characterized by different spectroscopic techniques and screened for antimicrobial activity against gram positive and gram-negative bacteria. Satisfactory results of antimicrobial activity were obtained with most of the compounds.

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